REMARKS

This Amendment responds to the January 9, 2004 Office Action in the above-referenced patent application. Claims 46 and 83 have been amended, 1-45, 50-69, 72, 77, and 82 have been corrected, and new claims 98-100 have been added. Accordingly, claims 46-50, 61-63, 70-71 and 73-76, 78-81, and 83-100 are currently pending, and claims 46-49, 70-71, 73-83, 85, 94, and 98-100 are under consideration.

1 The Pending Claims Satisfy the Requirements for Patentability Under 35 USC § 103

The striking and unexpected results demonstrated by applicants at page 47 of the application, and reproduced below, reveal an invention that opens an entire new avenue of drug development:

ANALGESIC EFFECT OF ENKEPHALIN CONJUGATES IN RATS				
Drug or Conjugate	Dose (mg/kg)	Number of Rats	Mean Analgesia As Compared with Morphine at 3 mg/kg	
			@ 5 min	@ 30 min
Morphine	3	8	100%	100%
Enkephalin	20	7	0%	0%
Cetyl-PEG-ENK	5	8	84%	75%
DHA-PEG-ENK	20	8	130%	67%
Cholesterol-PEG-ENK	5	8	80%	68%
Linolenic-PEG-ENK	10	8	77%	73%

These data illustrate that not only did the conjugation using the applicants claimed invention result in central nervous system delivery of enkephalin (which showed no substantial effect in an unconjugated state), but also that the applicants administration of amphiphilically conjugated enkephalin resulted in central nervous system activity that was still present after 30 minutes.

Even considering for the sake of argument, that the capability of effecting analgesia in the central nervous system was inherently present in the compounds described by Ekwuribe et al. (the "Ekwuribe compounds"), nothing in Ekwuribe et al. or in the the other references cited by the Examiner[1] teaches or suggests that the Ekwuribe compounds can be administered to a subject and thereafter traverse the blood-brain barrier to enter the central nervous system and mediate analgesia.

[1] See the Office Action at sections 8-15.

One of skill in the art might, under this hypothetical, be motivated to inject the compounds described by Ekwuribe into the central nervous system to mediate analgesia. Or, a skilled artisan might be motivated to administer the Ekwuribe compounds peripherally to induce a peripheral effect. However, one skilled in the art would not be motivated to administer the Ekwuribe compounds peripherally in order to induce an effect that is mediated in the central nervous system. Alternatively stated, a skilled artisan ***would not be motivated to select a subject in need of an effect mediated in the central nervous system for a peripheral administration of the Ekwuribe compounds***. Nothing in Ekwuribe et al. or in the remaining references cited by the Examiner suggests such selection.

Although the applicants maintain that the claims as previously presented are allowable, in order to expedite allowance, the applicants have amended the claims to emphasize this "selection aspect" of the invention, i.e., the claims as amended require the selection for peripheral administration of a subject needing central nervous system-mediated effect, a requirement that is not taught or suggested by the cited references.

1.1 Claim Amendments

Thus, claim 46 has been amended to recite:

> A method for inducing analgesia in a subject, wherein the subject is in need ~~thereof~~ of analgesia mediated in the central nervous system, the method comprising delivering across the blood brain barrier of the subject, into the subject's central nervous system ...

This amendment is supported, inter alia, by the data reproduced above, as well as Section 5.9 of the specification showing binding in brain sections consistent with distribution of μ opioid receptors, and at page 4, line 11, where the specification states:

> There is therefore a need for pharmaceutical compositions which can ... penetrate through the BBB in sufficient amounts and at sufficient rates to be efficacious.

See also page 6, line 4, stating:

> There is therefore a need in the art for means for enabling therapeutic agents, such as peptides, to cross the BBB in a controlled manner which permits accumulation of sufficient quantities of the therapeutic in the brain to induce the desired therapeutic effect.

Other support can be found throughout the specification, and indeed, the amendment is in line with the entire thrust of the application. Similar amendments were made to claim 83 based on the same support.

1.2 New Claims

In addition to the amendments made to claims 46 and 83, new claims 98, 99 and 100 were added. Claim 98 recites:

> 98. (new) A method for inducing analgesia in a subject, wherein the subject is in need of analgesia mediated in the central nervous system, the method comprising delivering across the blood brain barrier of the subject into the subject's central nervous system an amphiphilic drug-oligomer conjugate comprising an opioid conjugated to an oligomer in an amount sufficient to effect central nervous system-mediated analgesia, wherein the oligomer comprises one or more lipophilic moieties coupled to one or more hydrophilic moieties, and ***wherein the conjugate traverses the blood brain barrier in an amount that is greater than the amount of a corresponding unconjugated control.***[2]

This claim emphasizes the aspect of the invention supported by the data reproduced above, in which conjugation results in an amount of conjugate traversing the blood brain barrier, which amount is greater than the amount of a corresponding on conjugated control, (i.e., the unconjugated parent compound). This claim ***includes*** opioids, such as those described by Yagi et al., which may already have some capacity to traverse the blood brain barrier, but requires improvement to this blood-brain barrier traversing capacity.

Claim 99 recites:

> 99. (new) A method for inducing analgesia in a subject, wherein the subject is in need of analgesia mediated in the central nervous system, the method comprising delivering across the blood brain barrier of the subject into the subject's central nervous system an amphiphilic drug-oligomer conjugate comprising an opioid conjugated to an oligomer in an amount sufficient to effect central nervous system-mediated analgesia, wherein the oligomer comprises one or more lipophilic moieties coupled to one or more hydrophilic moieties, and wherein ***a corresponding unconjugated control does not cross the blood-brain barrier in an analgesically effective amount.***[3]

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[2] Emphasis added.
[3] Emphasis added.

Claim 99 emphasises the aspect of the invention in which "a corresponding unconjugated control does not cross the blood-brain barrier in an analgesically effective amount." This claim ***excludes*** opioids, such as those described by Yagi et al., which may already have some substantial capacity to traverse the blood brain barrier. This claim is supported, *inter alia*, by the data reproduced above.

> 100. (new) A method for inducing analgesia in a subject, wherein the subject is in need of analgesia mediated in the central nervous system, the method comprising delivering across the blood brain barrier of the subject into the subject's central nervous system an amphiphilic drug-oligomer conjugate comprising an opioid conjugated to an oligomer in an amount sufficient to effect central nervous system-mediated analgesia, wherein the oligomer comprises one or more lipophilic moieties coupled to one or more hydrophilic moieties, and ***wherein the conjugate crosses the BBB in a controlled manner which permits accumulation of sufficient quantities of the therapeutic in the brain to induce analgesia***.[4]

Claim 100 emphasises the aspect of the invention in which "the conjugate crosses the BBB in a controlled manner which permits accumulation of sufficient quantities of the therapeutic in the brain to induce analgesia." This claim is supported, *inter alia*, by the data reproduced above, as well as the specification at page 6, line 4, which states:

> There is therefore a need and the art for means for enabling therapeutic agents, such as peptides, to cross the BBB ***in a controlled manner which permits accumulation of sufficient quantities of the therapeutic in the brain to induce the desired therapeutic effect***.[5]

1.3 Discussion of Patentability of Amended and Newly Submitted Claims

While it is true that "[t]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer,"[6] the discovery of a previously unappreciated property can and oftent does result in patentable subject matter when "there is some other inventive concept in its application."[7] *Schering Corp. v. Geneva Pharms., Inc.*, while dealing with anticipation, is nonetheless instructive:

> Finally, this court's conclusion on inherent anticipation in this case does not preclude patent protection for metabolites of known drugs. With proper claiming, patent protection is available for metabolites of known drugs....

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[4] Emphasis added.
[5] Emphasis added.
[6] *Atlas Powder Co. v. IRECO Inc.*, 190 F.3d 1342, 1347, 51 U.S.P.Q.2D (BNA) 1943, 1947 (Fed. Cir. 1999).
[7] *Parker v. Flook*, 437 U.S. 584, 594, 57 L. Ed. 2d 451, 98 S. Ct. 2522 (1978).

> But those metabolites may not receive protection via compound claims. In this case, for instance, claims 1 and 3 broadly encompass compounds defined by structure only. Such bare compound claims include within their scope the recited compounds as chemical species in any surroundings, including within the human body as metabolites of a drug. As this case holds, these broad compound claims are inherently anticipated by a prior art disclosure of a drug that metabolizes into the claimed compound.
>
> A skilled patent drafter, however, might fashion a claim to cover the metabolite in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and isolated form, as in *Kratz and Bergstrom*, or as a pharmaceutical composition (e.g., with a pharmaceutically acceptable carrier). The patent drafter could also claim a method of administering the metabolite or the corresponding pharmaceutical composition. The '233 patent would not provide an enabling disclosure to anticipate such claims because, for instance, the '233 patent does not disclose isolation of DCL.[8]

Similarly, the applicants in the present case are not simply claiming the administration of amphiphilically conjugated enkephalins, but are claiming a specific use of amphiphilically conjugated enkephalins, involving peripheral administration to effect central nervous system analgesia, a method made possible by a property of the conjugated enkephalins that was surprisingly discovered after the invention described in of Ekwuribe et al. The claimed method is not taught or suggested by the cited references, and the cited references would not motivate one of skill in the art to select a subject in need of central nervous system-mediated analgesia for peripheral administration of conjugated enkephalins, as recited in the applicants' claims.

Furthermore, as emphasized by the applicants' former patent counsel in the March 5, 2004 telephone interview with Examiner Bennett Celsa, the MPEP states that "[O]bviousness cannot be predicated on what is not known at the time in invention is made, even if the inherency of at a certain feature is later established." Consequently, the 35 USC § 103 rejections based on the inherency of the later discovered capacity for amphiphilically conjugated peptides to traverse the blood brain barrier was inconsistent with current Patent Office procedure as set forth in the MPEP.

For the foregoing reasons, the applicants contend that the 35 USC § 103 rejections set forth in sections 8 and 9 of the Office Action have been overcome, and that the claims are now in condition for allowance.

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[8] *Schering Corp. v. Geneva Pharms., Inc.*, 339 F.3d 1373, 1381 (Fed. Cir., 2003).

2 The Claims as Amended Overcome the Obviousness-Type Double Patenting Rejections of Sections 10, 11, 12 and 13 of the Office Action

Each of the obviousness-type double patenting rejections set forth in sections 10, 11, 12, and 13 of the Office Action depends on the contention that the inherent ability of the conjugates to traverse the blood brain barrier renders the claimed invention obvious. However, the arguments and amendments discussed in Section 1 above show that the pending claims cannot be deemed invalid based on the doctrine of inherency. The obviousness-type double patenting rejections of sections 10, 11, 12, and 13 of the Office Action are overcome based on the same arguments and amendments, and the pending claims are in condition for allowance.

3 The Obviousness-Type Double Patenting Rejections of Sections 14 and 15 of the Office Action are Invalid Because They are Based on a Sister Divisional Application

As the applicants' former patent counsel discussed with the Examiner in the telephone interview of March 5, 2004, the Ekwuribe et al. reference (09/429,798) forming the basis of the obviousness-type double patenting rejections of sections 14 and 15 of the Office Action, is a divisional sister application to the present application, and is therefore technically unavailable for use as a reference against the present application. The applicants appreciate the Examiner's agreement in the telephone interview that he will, upon verification of the relationship between the applications, withdraw these two rejections.

4 Conclusion

Based on the amendments and arguments presented above, the applicants believe that the pending claims are is now in condition for allowance. If the Examiner has any questions about the present Amendment, a telephone interview is requested.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 13-4365.

Respectfully submitted,

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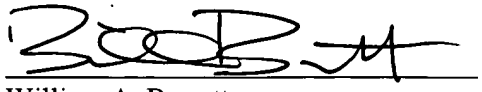
Date: July 8, 2004

By: 

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